Pediatric Withdrawal Identification and Management

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Abstract

Sedation administered by continuous intravenous infusion is commonly used in the pediatric intensive care unit to facilitate and maintain safe care of children during critical illness. Prolonged use of sedatives, including opioids, benzodiazepines, and potentially other adjunctive agents, is known to cause withdrawal symptoms when they are stopped abruptly or weaned quickly. In this review, the common signs and symptoms of opioid, benzodiazepine, and dexmedetomidine withdrawal will be discussed. Current tools used to measure withdrawal objectively, as well as withdrawal prevention and management strategies, will be discussed.

Keywords

- pediatric withdrawal
- pediatric narcotic withdrawal
- pediatric benzodiazepine withdrawal
- dexmedetomidine withdrawal

Introduction

Continuous intravenous (IV) sedation is commonly used in the pediatric intensive care unit (PICU) to facilitate safe care during critical illness. Historically, the most common agents used are opioids such as fentanyl and morphine and benzodiazepines, including midazolam and lorazepam.[1] Other adjunctive agents are often added into the regimen due to the development of tolerance or to minimize the total dosage of opioids and benzodiazepines. A survey of sedation practices of 20 PICUs in the United Kingdom reported the use of 14 different IV agents, as well as 10 different enteral medications.[2]

Along with the development of tolerance to sedative agents, withdrawal syndromes have been well described in the literature.[1,3] Much progress has been made in understanding the mechanisms of withdrawal in children, but the assessment, prevention, and management of iatrogenic withdrawal continue to be challenging. Adding to the challenge is that newer medications such as dexmedetomidine originally thought to help mitigate withdrawal syndromes may be associated with its own withdrawal syndrome.[4–6] This review article will discuss common signs and symptoms of pediatric withdrawal, assessment tools available to measure withdrawal, and management strategies for treating withdrawal signs and symptoms.

Withdrawal Definitions

It is important to have consistent definitions when describing the terminology associated with withdrawal. Currently

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published definitions refer specifically to withdrawal from opioids and benzodiazepines.

Addiction

A primary, chronic neurobiological disease with genetic, psychosocial, and environmental factors including one or more of the following behaviors: impaired control over drug use, continued use despite harm, and craving.[7]

Physical Dependence

An adaptive state manifested by a drug class–specific withdrawal syndrome produced by abrupt cessation, rapid reduction in dosage, decreasing blood level of the drug, and/or administration of an antagonist.[7]

Tolerance

A state of adaptation in which exposure to a drug induces change, resulting in a lessening of one or more of the drug's effects over time, necessitating larger doses to maintain the same effect.[7]

Withdrawal

A clinical response to the cessation of an opioid or benzodiazepine medication after continuous prolonged exposure. Manifestations typically occur between 8 and 48 hours after discontinuation.[8]

Tachyphylaxis

A rapid loss of drug effect caused by compensatory neurophysiologic mechanisms.[3]

Opioid and Benzodiazepine Analgesia Physiology

The physiology of opioid analgesia is well understood. Three opioid receptors sensitive to specific endogenous and exogenous opioids are responsible for the differing effects between opioids because of their differing agonistic and antagonistic properties. Receptors produce analgesia through inhibition of synaptic transmission. Chronic stimulation of these receptors leads to desensitization and other mechanisms limiting receptor number and accessibility. The significance of this in the development of tolerance is unclear. When opioid administration ceases, withdrawal occurs due to rebound increase in neurotransmitter release, which increases nervous system stimulation. Further effects result from withdrawal-induced hyperexcitability of many brain regions.[1,9]

The mechanism of benzodiazepine sedation is also well understood; gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that localizes to ~30% of synapses.[10] Benzodiazepines modulate the sensitivity of GABA-A receptor for GABA, hyperpolarizing the neuron, which leads to sedation and anxiolysis. While tolerance and dependence are recognized, none of the various effects of chronic administration appear to directly cause tolerance. Cessation of chronic benzodiazepine administration decreases the efficacy of available GABA at the receptor, leading to disinhibition of the central nervous system (CNS).[1,11]

Use of these medications for more than a few days may lead to tolerance. This in turn leads to more medication being needed to maintain the desired effects, which leads to physical dependence. Continued administration is required to prevent withdrawal syndrome.[12]

Risk Factors for Withdrawal

Duration of infusion and higher cumulative doses of medications have been described as primary risk factors for development of withdrawal syndromes.[13] Opioid tolerance rarely develops after therapy for less than 72 hours.[3] In 2007, Ista et al[8] reviewed 20 pertinent journal articles regarding withdrawal symptoms from sedation with opioids and benzodiazepine. They concluded that patients receiving benzodiazepines and/or opioids for five days or longer are at risk for developing withdrawal syndrome.

Additional risk factors for the development of opioid tolerance have not been clearly identified. Animal data suggest that age may play a role, as preterm neonates metabolize morphine to morphine-3 glucuronide (M3G) with antiopioid effects, whereas older age groups form morphine-6 glucuronide (M6G) with potent analgesic effects, with both metabolites having longer half-lives than morphine. Accumulation of M3G in preterm infants antagonizes the effects of morphine and contributes to opioid tolerance. Gender studies in animals suggest development of tolerance is greater in males than in females; however, this is not yet supported in human research.[3]

There have been no systematic investigations of different agents; however, drugs that cause opioid receptor internalization, decreased receptor phosphorylation by G protein–coupled receptor kinases, and less downregulation of opioid receptors are associated with less tolerance. For example, it is known that the *N*-methyl-aspartate (NMDA) receptor antagonist effects and mu (μ) opioid receptor desensitization caused by methadone explain its lower tolerance potential compared with morphine.[3]

Common Signs and Symptoms of Withdrawal

Benzodiazepines and opioids share some overlapping symptoms such as agitation, anxiety, tremors, insomnia, and sweating. Dexmedetomidine withdrawal, which is discussed below, shares some common CNS symptoms seen in opioid and benzodiazepine withdrawal as well (►**Table 1**).

Opioid

Symptoms of opioid withdrawal have been well described in the literature and include manifestations of the CNS, autonomic nervous system, and gastrointestinal system.

Symptoms of CNS overstimulation include tremors, increased muscle tension, anxiety, restlessness, irritability, and insomnia. The most frequent gastrointestinal symptoms of opioid withdrawal are vomiting and diarrhea. Autonomic manifestations include fever, perspiration, sneezing, yawning, tachycardia, and hypertension.[1,13,14]

Table 1 Signs and symptoms of withdrawal

Opioid	Benzodiazepine	α_2-Adrenergic agonist
Tremors	Tremors	Agitation
Restlessness	Anxiety	Blank staring
Irritability	Involuntary muscle movement	Decreased communication
Insomnia	Irritability	Asymmetric pupils
Vomiting	Perspiration	Facial drooping
Diarrhea	Insomnia	Abnormal chewing motions
Fever	Seizures	Rhythmic jerking movements
Perspiration	Hallucinations	Hypertonicity
Sneezing		
Yawning		
Tachycardia		
Hypertension		

Benzodiazepine

There has been limited research in pediatrics regarding benzodiazepine withdrawal; much is extrapolated from the adult literature. Symptoms of benzodiazepine withdrawal include anxiety, tremors, and other involuntary muscle movements, irritability, perspiration, and insomnia.[8,12] Diarrhea does not typically occur in benzodiazepine withdrawal. Seizures and hallucinations have also been described in benzodiazepine withdrawal in PICU patients.[8]

Issues That May Mask Signs and Symptoms

Many signs and symptoms of withdrawal may mimic other conditions, especially in children requiring PICU management. Withdrawal should be a diagnosis of exclusion after alternate causes of the offending symptoms are ruled out.[10] Pathophysiology that may cause signs and symptoms such as tachycardia, agitation, or fever include inadequate sedation, sepsis, and cardiovascular or neurologic pathology. Delirium must also be considered on the differential list.

Dexmedetomidine Withdrawal

Dexmedetomidine has increased in popularity as an adjunctive sedative agent for long-term use in the PICU. Dexmedetomidine is currently Food and Drug Administration (FDA) approved in the United States for short-term continuous infusion of less than 24 hours in adults, but its use has crossed over into pediatrics because of its favorable attributes of a short half-life, ease of titration, and limited effects on hemodynamic and respiratory function.[15] As an α-2 adrenergic agonist, it works centrally to produce sedation, anxiolysis, and analgesia.[4] The most common known adverse effects of dexmedetomidine by infusion are hypotension and bradycardia.[16] Transient hypertension has been noted usually in the setting of loading dosing due to vasoconstriction by stimulation of peripheral postsynaptic α adrenergic receptors.[16]

Dexmedetomidine is often initiated to mitigate the effects of escalating doses of traditional opioids and benzodiazepines due to tolerance over time. Its enhanced sedative effect allows for downward titration of the other agents in many patients. However, dexmedetomidine use for a prolonged period may result in its own withdrawal syndrome. To date, there are no randomized controlled clinical trials (RCTs) studying the long-term use of dexmedetomidine in critically ill children. Most available information has been described in retrospective case reviews. These reviews have primarily focused on the efficacy of sedation and have not focused on how to terminate the drug or its effects postdiscontinuation.

Based on its pharmacologic properties that are similar to clonidine, the potential for dexmedetomidine withdrawal should be expected, but it has been underappreciated until its long-term use has become more widespread. Several retrospective case series have highlighted potential signs and symptoms of dexmedetomidine withdrawal. Miller et al[5] reported the experience of a 2-year-old with a congenital heart disease repair who received dexmedetomidine continuously for 263 hour as an adjunct to fentanyl and midazolam continuous infusions. The infusion of 0.7 μg/kg/h was abruptly discontinued at 263 hour. At approximately 5 hours after infusion discontinuation, the patient began to experience neurological symptoms including agitation, blank staring, decreased communication, and asymmetric pupils. The patient was treated with rescue doses of morphine and lorazepam to treat possible opioid or benzodiazepine withdrawal with minimal change in signs and symptoms except for improvement of the agitation. The authors attributed the signs and symptoms to dexmedetomidine withdrawal given the timing of onset of symptoms, which closely mimicked those reported with clonidine withdrawal.[5]

Honey et al[6] completed a retrospective review of 36 patients that received 41 continuous dexmedetomidine infusions in one academic medical center over a 1-year period. Their main purpose was to identify the incidence and types of adverse events associated with the use of dexmedetomidine by continuous infusion and to identify

potential risk factors for such events. Adverse events were defined as hypotension, rebound hypertension, bradycardia, apnea, or neurological abnormalities. Neurologic abnormalities were further defined as change in verbal or motor functioning or increased agitation from baseline. The duration of infusion ranged from 6 hours to 11 days. Four of the 36 patients (9.8%) experienced neurological abnormalities. Two of the patients were tapered off their infusion, while two were stopped abruptly. Neurologic symptoms including decreased verbal communication, facial drooping, pupillary changes, agitation, abnormal chewing motions, rhythmic jerking movements, and abnormal head turning were noted to commence at the time when the infusion was being tapered or after discontinuation. The only statistically significant risk factor for withdrawal was length of stay in intensive care unit, although there were overall more adverse events in patients who received larger cumulative doses of dexmedetomidine or had a longer duration of therapy.[6]

These case reviews highlight potential signs and symptoms of dexmedetomidine withdrawal. The symptoms appear to be mainly CNS specific (►**Table 1**). It is not clear if signs and symptoms of dexmedetomidine withdrawal are correlated to infusion duration, total cumulative dose, or abrupt cessation, or if simultaneous weaning of opioids and/or benzodiazepines affects the symptoms seen. There is anecdotal evidence that abrupt cessation of the medication may be associated with more withdrawal symptoms.[5,6,17] The potential good news about dexmedetomidine withdrawal is that symptoms appear to be time limited. Miller et al[5] noted that patients' symptoms resolved within 2 days of onset without any intervention. However, there is no information whether there are any long-term effects of dexmedetomidine withdrawal on the CNS.

Withdrawal Assessment Tools

There are a multitude of tools currently being used to assess and determine effects on the pediatric patient experiencing opioid and/or benzodiazepine withdrawal. The signs and symptoms assessed by the tools are usually of three types: those that occur from overstimulation of the CNS, symptoms of autonomic dysregulation, and gastrointestinal dysfunction.[8] Accuracy and standardization of these assessments are the baseline for developing effective prevention and treatment plans and research into best practices. Concerns surrounding the use of assessment tools include differences in opioid and benzodiazepine withdrawal symptoms, the span of ages in the pediatric population, tool validation with the different ages, tool complexity, and time for completion.

One of the first tools developed, which is also still extensively used, is the Neonatal Abstinence Score (NAS). Developed in 1975 by Finnegan et al, this tool measures the presence and severity of 31 CNS, gastrointestinal, and metabolic/vasomotor/respiratory withdrawal signs and symptoms in the newborn or infant exposed to narcotics in utero due to maternal addiction. The patient's withdrawal is labeled as mild, moderate, or severe depending on the total score.[18,19] Though the NAS was originally developed to assess patient withdrawal from in-utero exposure to opioids, it has been successfully used in neonates and infants with iatrogenic opioid exposure. The NAS has strong inter-rater reliability and validity for assessment of withdrawal signs and symptoms in many neonatal populations.[18,19] Due to its effectiveness, the NAS has also been used in pediatric patients. However, reliability and validation are not established in this population and it may be too complicated for pediatric use.

Other tools are available including the Sedation Withdrawal Score (SWS) created by Cunliffe et al,[20] which scores 12 signs of withdrawal with values between 0 and 2 in an attempt to quantify withdrawal severity. Information on decreasing sedation doses is also included with this tool. However, scarce support for tool sensitivity, validity, and reliability is available.[8,20] The Opioid-Benzodiazepine Withdrawal Scale (OBWS), developed by Franck et al,[14] is a 21-item checklist for determining frequency and severity of withdrawal symptoms. It correlated well with nursing judgment, though it has limited specificity and sensitivity measurements.[8,14] The Neonatal Narcotic Withdrawal Index and the Modified Narcotic Abstinence Scale were derived from neonatal withdrawal assessment, so pediatric use may be inappropriate.[3,21]

The only tool validated for assessment of opioid withdrawal in the pediatric patient is the Withdrawal Assessment Tool-1 (WAT-1). Conceived by Franck et al,[22] the WAT-1 measures 11 gastrointestinal, autonomic, and CNS signs and symptoms of opioid withdrawal, and scores them from 0 to 1 or 0 to 2, depending on the type of symptom and its severity. A score of 3 or greater indicates that signs of opioid withdrawal are present. The severity of the withdrawal is not categorized. The WAT-1 has high specificity and sensitivity. It has undergone validation in many pediatric care centers. The information obtained from use of the WAT-1 is generalizable, and its use may assist in best practice research for withdrawal symptom management and prevention. Continued concerns related to use of the WAT-1 involve the differing signs and symptoms related to opioid versus benzodiazepine exposure and whether the WAT-1 captures signs and symptoms of both opioid and benzodiazepine withdrawal.[23]

The Sophia Observation withdrawal Symptoms scale (SOS) was crafted by Ista et al[24] to assess withdrawal symptoms in the PICU patient. The 15 items on the SOS characterize both opioid and benzodiazepine withdrawal signs and symptoms. The tool was developed using expert opinion and multidimensional scaling. The multidimensional scaling analysis was used to detect meaningful dimensions of observed similarities and dissimilarities between the withdrawal symptoms. This analysis suggests that variation of withdrawal symptoms between individuals will still occur.[24] Consistency and concurrent validity of this tool are considered sound.[25]

Prevention and Treatment of Withdrawal in Pediatrics

Prevention of withdrawal begins with recognition that with the administration of opioids or benzodiazepines in the PICU

setting, there is the potential for tolerance, physical dependence, and withdrawal. Understanding withdrawal is the key to prevention, and of course prevention ideally begins with minimizing the use of opioids and benzodiazepines when possible. Realistically, the use of opioids and benzodiazepines in the PICU setting is relatively unavoidable given the high acuity and advanced technology in use, including mechanical ventilation and invasive vascular access devices and drains.[17]

If a child is considered at risk for withdrawal, the most common approaches for the prevention/treatment of withdrawal symptoms include gradual weaning of the continuous infusions by predetermined percentages (usually 10–20% of the dose at the time when the wean is started) every 24 to 48 hours, or transitioning to a long-acting opioid and/or benzodiazepine. Other strategies such as daily interruption of sedatives, nurse-controlled sedation, sequential rotation of analgesics, or the use of epidural/intrathecal opioids have been shown to delay the onset or decrease the severity of withdrawal symptoms.[3]

A meta-analysis by Oschman et al[26] discusses the choice of pharmacotherapy for prevention of withdrawal symptoms through the use of transition agents. The most commonly used agents are morphine, methadone, diazepam, lorazepam, and phenobarbital, with methadone being the most common opioid conversion agent. Methadone is an effective analgesic with a prolonged half-life, which inhibits tolerance through multiple mechanisms and is increasingly being used for opioid withdrawal in children.[3] Methadone conversion is at times challenging, with multiple conversion methods noted in the literature.[27] Lorazepam is most commonly used for midazolam conversion and is a more straightforward conversion.

Methadone Conversions

The two main approaches to initial methadone dosing are weight-based and formula-based strategies. Johnson et al[27] evaluated the published methadone dosing strategies of four weight-based and three formula-based dosing strategies. The weight-based approaches suggest calculating initial methadone dosing based on 0.05 mg/kg or 0.10 mg/kg, whereas the formula-based approach suggests considering the current rate of fentanyl or morphine infusion and multiplying that dose by 0.10 mg/kg to determine the total daily starting dose. Johnson et al[27] found that all three formula-based strategies had different potentially confusing formulas. Each strategy, regardless of initial dose, suggested different routes of administration, different approaches to weaning off the original short-acting medication, and differences in frequency and duration of treatment.

Johnson et al[27] also reported on a prospective randomized comparison of the two approaches and reported no difference found in the development of withdrawal. There was, however, a significant 10-fold discrepancy in the initial dose recommended, with the formula-based dose being 10 times higher than the weight-based dose. There was a slight increase but no statistical difference in the number of patients experiencing over sedation requiring a dose of methadone to be held. The authors concluded that since the risk of calculation error was greater with formula-based dosing and that there was no statistical benefit in terms of reduction of symptoms or duration of treatment that a weight-based dose should be initiated and titrated accordingly.[27]

Equipotent dose calculations may also be used when converting from morphine or fentanyl to methadone. When administered in comparable doses, IV methadone has equianalgesic properties to IV morphine. Several different opioid conversion tables are available for determination of equianalgesic doses. A common equipotent conversion for fentanyl is 0.001 mg/kg = 0.10 mg/kg methadone and common conversion for morphine is 0.10 mg/kg = 0.10 mg/kg methadone.[27] Problems arise when converting from IV to enteral dosing as the equianalgesic conversion from IV methadone to enteral methadone is generally not thought to be equivalent.[27] Lexicomp suggests a parenteral to enteral conversion of a parenteral:oral ratio of 1:2.[28] Recent studies in both adults and children have identified that there is a wide discrepancy in dosing depending on what conversion table is used. Based on these recent findings, the routine use of opioid conversion tables in clinical practice is not recommended.[27]

Adjunct Agents

Clonidine and dexmedetomidine have been identified as potentially useful when used as bridging medication adjuncts to standard therapy for withdrawal by blunting withdrawal symptoms without causing respiratory depression, permitting shorter opioid tapering schedules, and also reducing overall opioid requirement.[26] Clonidine is routinely used in adults as an adjunct treatment for withdrawal symptoms. It is effective both enterally and transdermally in the form of a patch daily. Dexmedetomidine may be given via continuous IV or subcutaneous (SQ) infusion. Preliminary studies have shown no reported adverse effects and similar withdrawal scores when SQ dexmedetomidine is administered at the same rate and dosing as IV dexmedetomidine.[26]

Concerns around adjunct or bridging medications include adding another medication that has the potential to cause its own withdrawal syndrome. There are no clear guidelines for the concurrent weaning of benzodiazepines and opioids or for weaning off the adjunct therapies. Authors investigating this issue suggest weaning from one medication at a time, but there is little evidence to support this practice.[26] With the growing evidence of dexmedetomidine withdrawal syndrome, gradual weaning of dexmedetomidine appears to be indicated when prolonged infusions of greater than 4 to 5 days are used.[4] Further studies around prolonged administration of dexmedetomidine in the PICU are needed, as well as elucidation of withdrawal signs and symptoms as discontinuation strategies evolve to mitigate the development of withdrawal symptoms.

Conclusion

Withdrawal syndromes continue to be a challenging issue in the PICU. Its mechanisms are well understood; however, the

prevention and adequate treatment of pediatric withdrawal have been elusive. As patient acuity continues to rise, the need for adequate and safe sedation continues to be at the forefront of therapy. The ability to totally prevent withdrawal after prolonged use of sedative medications in critically ill children may be unrealistic. Newer agents introduced into the PICU have not been successfully integrated into sedative regimens to make a major impact on preventing or mitigating the development of opioid and benzodiazepine withdrawal. Further studies of sedative regimens are sorely needed as are studies on how to best wean sedative medications. Improved discernment of assessment tools for differentiating between opioid and benzodiazepine withdrawal symptoms is needed as is further validation of these tools in multicenter PICU populations. Nurses are in a unique position to observe and assess the PICU patient over time. Nurses need to take the lead in managing their patients' sedation needs and become proactively involved in developing improved management and weaning strategies based on current evidence as well as participate in clinical research to improve the care of critically ill pediatric patients that require sedation.

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